NON-PROFIT
Docket No.: **201040/1020**

Applicant or Patentee : Maqsudul Alam and Randy Larsen
Serial or Patent No. : 09/455,978
Filed or Issued : December 6, 1999
For : HEME PROTEINS HEMAT-*HS* AND HEMAT-*BS* AND THEIR USE IN MEDICINE AND MICROSENSORS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF CONCERN : **University of Hawaii**
ADDRESS OF CONCERN : **Office of Technology Transfer and Economic Development**
2800 Woodlawn Drive, Suite 280
Honolulu, Hawaii 96822

TYPE OF ORGANIZATION :

[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)
[ ] NONPROFIT SCIENTIFIC OR EDUCATION UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA **(NAME OF STATE)** **(CITATION OF STATUTE)**
[ ] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA **(NAME OF STATE)** **(CITATION OF STATUTE)**

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled **HEME PROTEINS HEMAT-*HS* AND HEMAT-*BS* AND THEIR USE IN MEDICINE AND MICROSENSORS** by inventor(s) **Maqsudul Alam and Randy Larsen** described in

[ ] the specification filed herewith
[X] U.S. Patent Application Serial No.: **09/455,978**
Filed: **December 6, 1999**
[ ] U.S. Patent No.:
Issued:

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).

NAME :
ADDRESS :

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME :
ADDRESS :

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING : **Glenn K. Nakamura**
TITLE OF PERSON OTHER THAN OWNER : **Associate Director**
ADDRESS OF PERSON SIGNING : **2800 Woodlawn Drive, Suite 280**
Honolulu, Hawaii 96822

SIGNATURE: _____ DATE: January 10, 2000

HEME PROTEINS HEMAT-*HS* AND HEMAT-*BS* AND THEIR USE IN MEDICINE AND MICROSENSORS

The subject matter of this application was made with support from the United States Government under Grant No. MSB960086 from the National Science Foundation. The United States Government may retain certain rights.

BACKGROUND OF THE INVENTION

Heme proteins such as hemoglobin and myoglobin play an essential role in stabilizing molecular oxygen for transport and storage. The oxygen carrying portion of the red blood cell is hemoglobin, a tetrameric protein molecule composed of two identical alpha globins (alpha 1, alpha 2), two identical beta globins (beta 1, beta 2) and four heme molecules. A heme molecule is incorporated into each of the alpha and beta globins to give alpha and beta subunits. Heme is a macrocyclic organic molecule that contains an iron atom at its center; each heme can combine reversibly with one ligand molecule, for example oxygen. In a hemoglobin tetramer, each alpha subunit is associated with a beta subunit to form two stable alpha/beta dimers, which in turn associate to form the tetramer (a homodimer). The subunits are noncovalently associated through Van der Waals forces, hydrogen bonds and salt bridges. Ligands, particularly oxygen, bind reversibly to the reduced form of the iron (ferrous, Fe^{2+}) in the heme. Other ligands which compete with oxygen for the heme group include carbon monoxide and nitric oxide.

It is not always practical to transfuse a patient with donated blood. The well known complications of blood transfusion namely incompatibility reactions, disease transmission, immunosuppression and the storage limitations of erythrocytes points to the need for the development of blood substitutes devoid of these shortcomings. In these situations, use of a red blood cell substitute is necessary. A "blood substitute" is a preparation that does not necessarily replace blood in all of its functions, but an emergency resuscitative fluid that is capable of efficiently transporting oxygen to tissue. This fluid, however, must be free of toxic side-effects, as well as of agents of disease such as bacteria and viruses.

For over 50 years, efforts directed to the development of a blood substitute have focused on hemoglobin (Hb). Hemoglobin (Hgb) is the oxygen-carrying component of